

In the Specification

On page 1 of the Specification, please replace paragraphs [0001] with the following amended paragraph.

[0001] This application claims priority to U.S. Provisional Patent Application No. 60/426,680 filed, November 15, 2002, titled "Kinase Modulators." This application is also claims priority to U.S. Provisional Patent Application No. 60/470,674 filed, May 14, 2003, titled "Kinase Modulators." Each of the ~~aforementioned~~ aforementioned patent applications is incorporated herein by reference for all purposes.

On page 2 of the Specification, please replace paragraph [0008] with the following amended paragraph.

[0008] Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth, associated with cancer. In addition to cancer altered kinase signaling is implicated in numerous other pathological diseases. These include, but not limited to: immunological disorders such as rheumatoid arthritis, graft-host diseases, multiple sclerosis, psoriasis; cardiovascular diseases such as ~~arteriosclerosis~~ atherosclerosis, myocardioinfarction, ischemia, stroke and restenosis; other inflammatory and degenerative diseases such as interbowel diseases, ~~osteoarthritis~~ osteoarthritis, macular degeneration, diabetic retinopathy. Therefore, both receptor and non-receptor protein kinases are attractive targets for small molecule drug discovery.

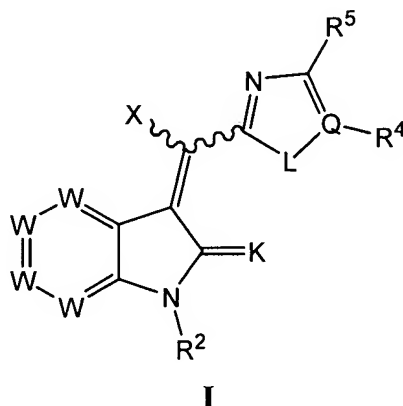
On page 5 of the Specification, please replace paragraph [0019] with the following amended paragraph.

[0019] The compositions of the invention are used to treat diseases associated with abnormal and or unregulated cellular activities, in particular those related to kinase activity, for example VEGF receptor 2 (Flk-1/KDR), FGFR1, and PDGFR (alpha and

beta). Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), immunological disorders such as rheumatoid arthritis, graft-host diseases, multiple sclerosis, psoriasis; cardiovascular diseases such as ~~arteriosclerosis~~atherosclerosis, myocardioinfarction, ischemia, stroke and restenosis; other inflammatory and degenerative diseases such as interbowel diseases, ~~osteoarthritis~~osteoarthritis, macular degeneration, diabetic retinopathy.

On pages 6-10 of the Specification, please replace paragraphs [0021]-[0038] with the following amended paragraphs.

[0021] Embodiment [0021]: The present invention comprises a compound for modulating kinase activity of Formula I,



or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

each W is independently N or CR¹;

each R¹ is independently selected from -H, halogen, trihaloalkyl, -CN, -NH₂, -NO₂, -OR⁶, -N=CNR⁶R⁷, -N(R⁶)C(=NR⁸)NR⁶R⁷, -SR⁶, -S(O)₁₋₂R⁶, -SO₂NR⁶R⁷, -CO₂R⁶, -C(O)NR⁶R⁷, -C(O)N(OR⁶)R⁷, -C(=NR⁸)NR⁶R⁷, -N(R⁶)SO₂R⁷, -NC(O)R⁶, -NCO₂R⁶, -C(O)R⁷, -R⁷, and -A-R⁷; provided at least one of R¹ is -A-R⁷, wherein, only for said at least one -A-R⁷, R⁷ must be an optionally substituted heteroalicyclic ring, and any nitrogen of said optionally substituted heteroalicyclic ring cannot be directly bound to A;

A is O, S(O)₀₋₂, and NR⁶;

L is O, S(O)₀₋₂, or NR³;

Q is C or N, when Q is N, then R⁴ does not exist;

R² and R³ are each independently -H or -R⁷;

R⁴ and R⁵ are each independently selected from -H, -OR⁶, -NR⁶R⁷, -S(O)₀₋₂R⁶, -SO₂NR⁶R⁷, -CO₂R⁶, -C(O)NR⁶R⁷, -N(R⁶)SO₂R⁶, -NC(O)R⁶, -NCO₂R⁶, -C(O)R⁷, -CN, -NO₂, -NH₂, halogen, trihalomethyl, and -R⁷; or

R⁴ and R⁵, when taken together, form a five or six-membered aromatic ring system containing between zero and two nitrogens, said five or six-membered aromatic ring system optionally substituted with between zero and four of R¹⁵;

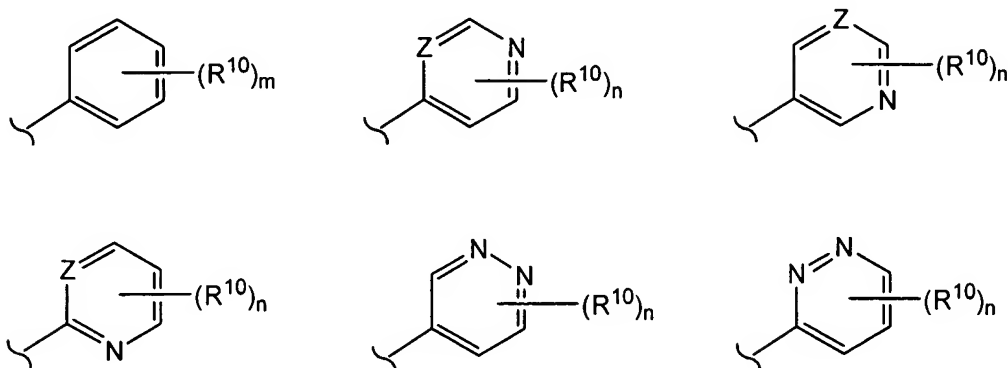
R⁶ is selected from -H, optionally substituted C₁₋₈alkyl, optionally substituted arylC₁₋₈alkyl, optionally substituted heterocyclylC₁₋₈alkyl, optionally substituted aryl, and optionally substituted heterocyclyl;

R⁷ is selected from -H, optionally substituted C₁₋₈alkyl, optionally substituted arylC₁₋₈alkyl, optionally substituted heterocyclylC₁₋₈alkyl, optionally substituted aryl, and optionally substituted heterocyclyl; provided that there are at least two carbons between any heteroatom of R⁷ and A or either nitrogen to which R² or R³ are attached; or

R⁶ and R⁷, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclic ring, said optionally substituted five- to seven-membered heterocyclic ring optionally containing at least one additional heteroatom selected from nitrogen, oxygen, sulfur, and phosphorus;

R⁸ is -H, -NO₂, -CN, -OR⁶, and optionally substituted C₁₋₈alkyl;

X is selected from one of the following six formulae:



wherein m is zero to five, n is zero to three, and Z is N or CR¹⁰;

R¹⁰ is selected from -H, halogen, trihalomethyl, -NH₂, -NO₂, -OR⁶, -N=CNR⁶R⁷, -NR⁶R⁷, -N(R⁶)C(=NR⁸)NR⁶R⁷, -SR⁶, -S(O)₁₋₂R⁶, -SO₂NR⁶R⁷, -CO₂R⁶, -C(O)NR⁶R⁷, -C(O)N(OR⁶)R⁷, -C(=NR⁸)NR⁶R⁷, -N(R⁶)SO₂R⁶, -NC(O)R⁶, -NCO₂R⁶, -C(O)R⁷, and R⁷;

K is O, S, or NR¹¹;

R¹¹ is selected from cyano, -NO₂, -OR⁶, -S(O)₁₋₂R⁶, -SO₂NR⁶R⁷, -CO₂R⁶, -C(O)NR⁶R⁷, -C(O)N(OR⁶)R⁷, -C(O)R⁷, and R⁶; and

each R¹⁵ is independently selected from -H, halogen, -NH₂, -NO₂, -OR⁶, -N=CNR⁶R⁷, -NR⁶R⁷, -N(R⁶)C(=NR⁸)NR⁶R⁷, -SR⁶, -S(O)₁₋₂R⁶, -SO₂NR⁶R⁷, -CO₂R⁶, -C(O)NR⁶R⁷, -C(O)N(OR⁶)R⁷, -C(=NR⁸)NR⁶R⁷, -N(R⁶)SO₂R⁶, -NC(O)R⁶, -NCO₂R⁶, -C(O)R⁷, and R⁷.

[0022] Embodiment [0022]: In one example, the compound is according to paragraph Embodiment [0021], wherein L is NR³.

[0023] Embodiment [0023]: In another example, the compound is according to paragraph Embodiment [0022], wherein K is either O or NR¹¹.

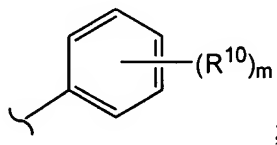
[0024] Embodiment [0024]: In another example, the compound is according to paragraph Embodiment [0023], wherein R² and R³ are each independently selected from -H and optionally substituted C₁₋₈alkyl, wherein substitution on the C₁₋₈alkyl of optionally substituted C₁₋₈alkyl is selected from -NH₂, -NO₂, -OR⁶, -N=CNR⁶R⁷, -NR⁶R⁷, -N(R⁶)C(=NR⁸)NR⁶R⁷, -SR⁶, -S(O)₁₋₂R⁶, -SO₂NR⁶R⁷, -CO₂R⁶, -C(O)NR⁶R⁷, -C(O)N(OR⁶)R⁷, -C(=NR⁸)NR⁶R⁷, -N(R⁶)SO₂R⁶, -NC(O)R⁶, -NCO₂R⁶, -C(O)R⁷, heterocyclic, alicyclic, and aryl.

[0025] Embodiment [0025]: In another example, the compound is according to paragraph Embodiment [0024], wherein R^2 and R^3 are -H.

[0026] Embodiment [0026]: In another example, the compound is according to paragraph Embodiment [0025], wherein only one of R^1 is $-A-R^7$, where A is selected from O, $S(O)_{0-1}$, and NR^6 ; and for $-A-R^7$, R^7 is an optionally substituted heteroalicyclic ring.

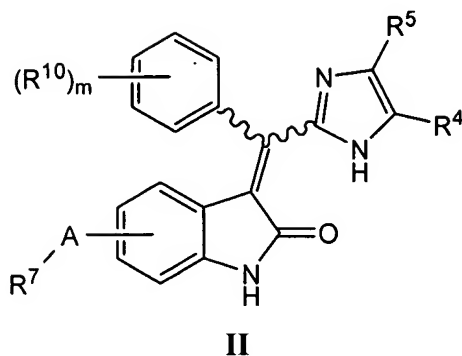
[0027] Embodiment [0027]: In another example, the compound is according to paragraph Embodiment [0026], wherein R^6 is selected from -H and C_{1-8} alkyl, said C_{1-8} alkyl optionally substituted with one or more groups each independently selected from $-NH_2$, $-NO_2$, $-OR^6$, $-N=CNR^6R^7$, $-NR^6R^7$, $-N(R^6)C(=NR^8)NR^6R^7$, $-SR^6$, $-S(O)_{1-2}R^6$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-C(O)N(OR^6)R^7$, $-C(=NR^8)NR^6R^7$, $-N(R^6)SO_2R^6$, $-NC(O)R^6$, $-NCO_2R^6$, $-C(O)R^7$, heterocyclic, alicyclic, and aryl; and R^7 of $-A-R^7$ is selected from the following optionally substituted heteroalicyclics: azetidine, perhydroazepinyl, piperidinyl, piperazinyl, azabicyclo[3.2.1]octyl, octahydro-cyclopenta[c]pyrrole, 2-oxopiperidinyl, 2-oxopyrrolidinyl, pyrrolidinyl, dihydropyridinyl, tetrahydropyridinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiamorpholinyl sulfone, and dioxaphospholanyl.

[0028] Embodiment [0028]: In another example, the compound is according to paragraph Embodiment [0027], wherein X is



m is 0 to 3, and R^{10} is selected from -H, halogen, $-NH_2$, $-NO_2$, $-OR^6$, $-N=CNR^6R^7$, $-NR^6R^7$, $-N(R^6)C(=NR^8)NR^6R^7$, $-SR^6$, $-S(O)_{1-2}R^6$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-C(O)N(OR^6)R^7$, $-C(=NR^8)NR^6R^7$, $-N(R^6)SO_2R^6$, $-NC(O)R^6$, $-NCO_2R^6$, $-C(O)R^7$, and optionally substituted C_{1-8} alkyl; said C_{1-8} alkyl optionally substituted with one or more groups each independently selected from $-NH_2$, $-NO_2$, $-OR^6$, $-N=CNR^6R^7$, $-NR^6R^7$, $-N(R^6)C(=NR^8)NR^6R^7$, $-SR^6$, $-S(O)_{1-2}R^6$, $-SO_2NR^6R^7$, $-CO_2R^6$, $-C(O)NR^6R^7$, $-C(O)N(OR^6)R^7$, $-C(=NR^8)NR^6R^7$, $-N(R^6)SO_2R^6$, $-NC(O)R^6$, $-NCO_2R^6$, $-C(O)R^7$, heterocyclic, alicyclic, and aryl.

[0029] Embodiment [0029]: In another example, the compound is according to paragraph embodiment [0028], of formula II:



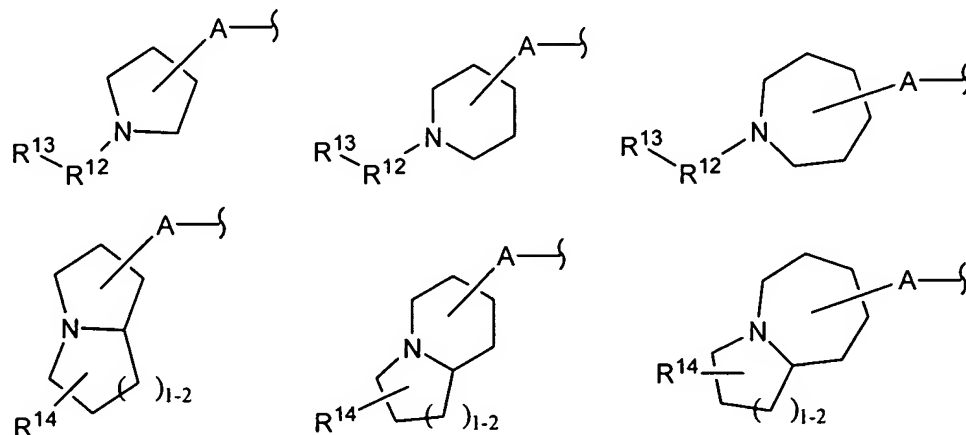
wherein:

A, R⁴, R⁵, R¹⁰, and m are as defined above;

R⁷ is selected from optionally substituted perhydroazepinyl, optionally substituted piperidinyl, optionally substituted pyrrolidinyl, and optionally substituted azetidiny; wherein the ring nitrogen of R⁷ is substituted with a group R¹²; and

R¹² is selected from -H, optionally substituted C₁₋₈alkyl, -SO₂R⁶, -SO₂NR⁶R⁷, -CO₂R⁶, -C(O)NR⁶R⁷, -C(O)R⁷, and an optionally substituted three- or four-carbon bridge between the ring nitrogen of R⁷ and a carbon vicinal to the ring nitrogen of R⁷; said three- or four-atom bridge optionally containing an oxygen in substitution for a carbon of the bridge.

[0030] Embodiment [0030]: In another example, the compound is according to ~~paragraph~~ Embodiment [0029], wherein -A-R⁷ is selected from the following formulae:

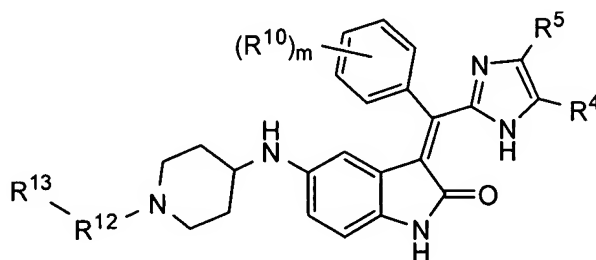


wherein R¹² is a C₁₋₄alkyl; R¹³ is selected from -H, an optionally substituted alkoxy group, an optionally substituted amino group, and an optionally substituted heteroalicyclic, with the proviso that a heteroatom of said optionally substituted alkoxy group, said optionally substituted amino group, or said optionally substituted heteroalicyclic cannot be attached

to a carbon of R^{12} which is directly attached to the ring nitrogen of R^7 ; and R^{14} is selected from -H, halogen, -NH₂, -NO₂, -OR⁶, -N=CNR⁶R⁷, -NR⁶R⁷, -N(R⁶)C(=NR⁸)NR⁶R⁷, -S(O)₀₋₂R⁶, -SO₂NR⁶R⁷, -CO₂R⁶, -C(O)NR⁶R⁷, -C(O)N(OR⁶)R⁷, -C(=NR⁸)NR⁶R⁷, -N(R⁶)SO₂R⁶, -NC(O)R⁶, -NCO₂R⁶, -C(O)R⁷, and optionally substituted C₁₋₆alkyl.

[0031] Embodiment [0031]: In another example, the compound is according to ~~paragraph~~ Embodiment [0030], wherein A is -NR⁶- where R⁶ is selected from -H and C₁₋₈alkyl, said C₁₋₈alkyl substituted with at least one of -CO₂H and -CO₂C₁₋₈alkyl.

[0032] Embodiment [0032]: In another example, the compound is according to ~~paragraph~~ Embodiment [0031], of formula **III**.



III

[0033] Embodiment [0033]: In another example, the compound is according to ~~paragraph~~ Embodiment [0032], wherein R¹² is a C₂₋₄alkyl; R¹³ is as defined above; R¹⁰ is selected from -H, halogen, perfluoroalkyl, -NH₂, -NO₂, -OR⁶, -N=CNR⁶R⁷, -NR⁶R⁷, -N(R⁶)C(=NR⁸)NR⁶R⁷, -SR⁶, -S(O)₁₋₂R⁶, -SO₂NR⁶R⁷, -CO₂R⁶, -C(O)NR⁶R⁷, -C(O)N(OR⁶)R⁷, -C(=NR⁸)NR⁶R⁷, -N(R⁶)SO₂R⁶, -NC(O)R⁶, -NCO₂R⁶, -C(O)R⁷; R⁴ and R⁵ are each independently selected from -H, halogen, and C₁₋₄alkyl; or R⁴ and R⁵ combined are an optionally substituted phenyl; and m is 0-3.

[0034] Embodiment [0034]: In another example, the compound is according to ~~paragraph~~ Embodiment [0033], wherein R¹² is an ethylene; R¹⁰ is halogen; R⁴ and R⁵ are each independently selected from -H, halogen, and C₁₋₂alkyl; and m is 1-3.

[0035] Embodiment [0035]: In another example, the compound is according to ~~paragraph~~ Embodiment [0034], wherein each R¹⁰ is independently selected from fluorine and chlorine; R⁴ and R⁵ are each independently selected from -H and C₁₋₂alkyl; and m is 1-3.

[0036] Embodiment [0036]: In another example, the compound is according to ~~paragraph~~ Embodiment [0035], wherein each R¹⁰ is independently selected from fluorine and chlorine; R⁴ and R⁵ are each independently selected from -H and -CH₃; and m is 1-2.

[0037] Embodiment [0037]: In another example, the compound is according to ~~paragraph~~
Embodiment [0036], wherein R^{10} is fluorine; R^4 and R^5 are each independently selected
from -H and -CH₃; and m is 1.

[0038] Embodiment [0038]: In another example, the compound is according to ~~paragraph~~
Embodiment [0021], selected from Table 1:

On pages 32-33 of the Specification, please replace paragraphs [0039]-[0046] with the following amended paragraphs.

- [0039] Embodiment [0039]: Another aspect of the invention is a pharmaceutical composition comprising a compound according to any one of ~~paragraph~~embodiments [0021]-[0038] and a pharmaceutically acceptable carrier.
- [0040] Embodiment [0040]: Another aspect of the invention is a metabolite of the compound or the pharmaceutical composition according to any one of ~~paragraph~~embodiments [0021]-[0039].
- [0041] Embodiment [0041]: Another aspect of the invention is a method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of the compound or the pharmaceutical composition according to any of ~~paragraph~~embodiments [0021]-[0039].
- [0042] Embodiment [0042]: Another aspect of the invention is the method according to ~~paragraph~~embodiment [0041], wherein the kinase is at least one of VEGF receptor 2 (Flk-1/KDR), FGFR1, and PDGFR (alpha and beta).
- [0043] Embodiment [0043]: Another aspect of the invention is the method according to ~~paragraph~~embodiment [0042], wherein modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.
- [0044] Embodiment [0044]: Another aspect of the invention is a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering, to a mammal in need thereof, a therapeutically effective amount of the compound or the pharmaceutical composition as described in any one of ~~paragraph~~embodiments [0021]-[0039].
- [0045] Embodiment [0045]: Another aspect of the invention is a method of screening for modulator of a kinase, the method comprising combining a compound according to any one of ~~paragraph~~embodiments [0021]-[0038], and at least one candidate agent and determining the effect of the candidate agent on the activity of said kinase.
- [0046] Embodiment [0046]: Another aspect of the invention is a method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount

of a composition comprising a compound according to any one of ~~paragraph~~embodiments [0021]-[0038] to a cell or a plurality of cells.

On page 39 of the Specification, please replace paragraphs [0075] with the following amended paragraph.

[0075] “Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that, with respect to any molecule described as containing one or more optional substituents, that only sterically practical and/or synthetically feasible compounds are meant to be included. “Optionally substituted” refers to all subsequent modifiers in a term, for example in the term “optionally substituted arylC₁₋₈ alkyl,” optional substitution may occur on both the “C₁₋₈ alkyl” portion and the “aryl” portion of the molecule; and for example, optionally substituted alkyl includes optionally substituted cycloalkyl groups, ~~which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*.~~ A list of exemplary optional substitution are listed below in the definition of “substituted.”